Melatonin, Circadian Rhythms, and Sleep

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Opinion statement

Experimental data show a close relationship among melatonin, circadian rhythms, and sleep. Low-dose melatonin treatment, increasing circulating melatonin levels to those normally observed at night, promotes sleep onset and sleep maintenance without changing sleep architecture. Melatonin treatment can also advance or delay the phase of the circadian clock if administered in the evening or in the morning, respectively. If used in physiologic doses and at appropriate times, melatonin can be helpful for those suffering from insomnia or circadian rhythm disorders. This may be especially beneficial for individuals with low melatonin production, which is established by measuring individual blood or saliva melatonin levels. However, high melatonin doses (over 0.3 mg) may cause side effects and disrupt the delicate mechanism of the circadian system, dissociating mutually dependent circadian body rhythms. A misleading labeling of the hormone melatonin as a "food supplement" and lack of quality control over melatonin preparations on the market continue to be of serious concern.

Introduction

The major structures of the biologic clock system—the pineal gland (epiphysis cerebri), the eyes, and the suprachiasmatic nuclei (SCN) of the hypothalamus—develop from the roof of the diencephalon. Together these structures allow the perception or the translation of changes in illumination caused by the earth's daily rotation and the organism's adaptive adjustment to it.

Melatonin (N-acetyl-5-methoxytryptamine) is the major hormone of the pineal gland and is secreted exclusively at night. The circulating amino acid L-tryptophan is the precursor of melatonin. Within cells in the pineal gland, it is converted to serotonin by a two-step process catalyzed by tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase. This process involves serotonin's N-acetylation, catalyzed by N-acetyltransferase, and its methylation by hydroxyindole-O-methyltransferase to produce melatonin. The hormone is released directly into the blood stream and the cerebrospinal fluid as it is synthesized and, because it is lipid soluble, it has ready access to every cell of the body. Approximately 50% to 70% of circulating melatonin is reportedly bound to plasma albumin; the physiologic significance of this binding is yet unknown. Inactivation of melatonin occurs in the liver where it is converted to 6-hydroxymelatonin by the P450-dependent microsomal mixed-function oxidase enzyme system. Most of the 6-hydroxymelatonin is excreted in the urine and feces as a sulfate conjugate (6-sulfatoxymelatonin), and a much smaller amount is excreted as a glucuronide. Some melatonin may be converted to N-acetyl-5-methoxykynurenamine in the central nervous system. Approximately 2% to 3% of the melatonin that is produced is excreted unchanged in the urine.

Regular activation of the pineal gland is defined by a periodic signal from SCN, which is the master biologic "clock." The SCN is active during the day and slowed down at night. A gradual reduction of SCN activity in the evening promotes the onset of nocturnal melatonin production. An abrupt imposition of bright light at night activates SCN and suppresses melatonin secretion. However, the exposure to darkness during the daytime does not induce melatonin production.

The temporal pattern of melatonin production by the pineal gland correlates with the timing of human sleep. The onset of nighttime melatonin secretion is initiated approximately 2 hours before individual's habitual bedtime and correlates with the onset of evening sleepiness [1,2••]. Observations in human infants also reveal that the timing of consolidation of nocturnal sleep coincides with the onset of rhythmic melatonin secretion, which occur when infants are approximately 3 months old. Furthermore, a typical reduction of melatonin secretion and sleep efficiency with aging could be related phenomenon.

Acute reduction in circulating melatonin levels after pinealectomy or from the suppression of melatonin production by, for example, treatment with adrenergic beta-blockers is reported to cause insomnia. In contrast, an increase in circulating melatonin induced by suppression of melatonin-metabolizing liver enzymes results in increased sleepiness.

Two major effects of melatonin treatment on sleep, a direct sleep promoting effect and a circadian phase shifting effect, may occur jointly or separately. Physiologic (3 to 5 μg/kg) and higher, pharmacologic oral doses of melatonin promote sleep onset or sleep maintenance when administered at different time of the day [2••,3–5, Class II]. The effect of melatonin on sleep initiation is typically manifest 30 to 60 minutes after the treatment. Studies in animal models suggest that this effect results from the activation of specific melatonin receptors. However, the exact brain structures conveying the sleep-promoting effect of melatonin remain to be elucidated. One of the candidate structures is SCN, although presence of melatonin receptors in thalamic nuclei and hindbrain may indicate that other sleep-related pathways may be involved. Melatonin appears to also produce an anxiolytic effect [6••, Class II], which could facilitate its hypnotic property. Compared with the majority of the existing hypnotics, the effects of melatonin on sleep initiation are not accompanied by any dramatic changes in electrophysiologic sleep architecture. Nevertheless, some decrease of stage 4 and an increase in stage 2 may occur in some individuals.

Although sleep-promoting effect of melatonin does not significantly depend on the time of administration, the timing of melatonin treatment is critical for its effect on the phase of the circadian clock. Hormone administration in the morning causes a phase delay, although evening treatment results in phase advance. Because sleep is under control of the circadian clock, these changes in the circadian phase will cause a delay in the onset of evening sleepiness or advance it to an earlier hour.

Treatment

Indications for melatonin therapy

- The sleep-promoting effect of melatonin is helpful in treating insomnia of different origin, especially in individuals with low melatonin secretion. The phase-shifting effect of melatonin can be beneficial to those suffering from circadian rhythm disorders, including phase delay or phase advance syndromes and blindness [7••, Class II]. The latter is associated with a "free-running" circadian rhythm (*ie,* with a period of more or less than 24 hours) and results in sleep alterations. This effect of melatonin can also help individuals with circadian rhythm alterations after transmeridian flight or shift work to resynchronize their circadian body rhythms with the environmental light-dark cycle. Moreover, patients with psychiatric and neurologic disorders, especially those experiencing anxiety, could benefit from melatonin treatment caused by hypnotic and anxiolytic effects of the pineal hormone. Melatonin treatment may also attenuate the subjective effects of drug withdrawal [6••, Class II].

Diet and lifestyle

- Despite melatonin being currently sold in the US under a peculiar label as a "dietary supplement," it is highly unlikely that any kind of diet can modify circulating melatonin levels. The amounts of melatonin in food are so negligibly low that in order to consume enough food to match the lowest physiologic oral dose used in human studies (*eg,* 0.1 mg) one would need to ingest hundreds of bananas, tomatoes, or hundreds of pounds of rice during one meal. Furthermore, melatonin is rapidly metabolized in the body, with a half-life less than an hour, making its accumulation over days

or weeks from consumption of melatonin-containing food impossible. Hence, dietary control of circulating melatonin levels is unrealistic, and calling the pineal hormone a food supplement is misleading.

- Under normal conditions, melatonin secretion does not occur during daytime and, thus, never coincides with bright environmental light. This temporal dissociation is also assured by nighttime melatonin secretion being significantly inhibited by the environmental light of relatively low intensity, within the range of regular room illumination. Thus, an irregular lifestyle or shift work would alter melatonin secretion and contribute to an overall disruption of the circadian rhythms and sleep.
- Melatonin administration induces high circulating levels of the hormone that could not be opposed by light, which permits these two stimuli to coincide in time. A combination of bright light and high circulating melatonin levels is likely to cancel or significantly attenuate the effect of melatonin treatment. More importantly, this could produce an adverse effect on the visual system, because melatonin has been reported to increase photoreceptor susceptibility to light-induced damage in animals [8] and may have a similar effect in humans [9••]. Thus, it is important not to expose an individual to bright light during melatonin treatment.

Pharmacologic treatment

Melatonin

Standard dosage

Physiologic doses of melatonin (0.1 to 0.3 mg) are efficient in promoting sleep and shifting the phase of the circadian clock in humans. After the administration of a 0.3-mg dose of the hormone, blood melatonin levels typically reach 100 to 150 pg/mL, which is similar to those observed normally in the middle of the night. However, in older individuals, the same dose can produce much higher melatonin levels, because of alterations in melatonin metabolism in the liver. Thus, even a relatively low melatonin dose may induce supraphysiologic circulating levels of the hormone in some people over 50 years of age, and the appropriate dose should be determined by measuring individual melatonin levels after treatment.

Typically, using an immediate-release ("fast") melatonin preparation can assure its overnight efficacy. In some patients, however, such fast-release preparations may not be able to sustain a high enough level of the hormone in the second half of the night. If this is the case and the symptoms of the sleep disorder include early morning awakening, an additional half-dose of melatonin (*eg,* 0.1 mg) on early morning awakening may be recommended.

Contraindications

There are no known contraindications in using physiologic doses of melatonin at nighttime in individuals with low melatonin secretion. However, melatonin deficiency and individual physiologic dose should be determined based on blood or saliva endogenous melatonin measurements at night or induced melatonin levels reached 1 hour after treatment.

Main drug interactions

Melatonin secretion depends on sympathetic innervation of the pineal gland. Thus, it can be inhibited by beta-blockers [10]. In contrast, alpha-2-adrenoceptor antagonists can enhance melatonin secretion at night [11].

Having a hypnotic property of its own, melatonin can also potentiate the effects of other hypnotic agents. A preliminary study showed that melatonin can facilitate a hypnotic effect of benzodiazepines and may allow reducing benzodiazepine therapeutic doses [12••].

Because serotonin is a precursor for melatonin synthesis in the pineal gland, substances that alter serotonin metabolism can affect melatonin production. So far, studies produced somewhat conflicting results on the effects of serotonin reuptake inhibitors, *eg,* fluvoxamine or fluoxetine, on melatonin synthesis; some studies reported the increase in melatonin production [13] and others documented

its decline [14••]. Such results may be partially explained by different effects of these drugs, ranging from increased extracellular serotonin levels to intracellular serotonin depletion, depending on the doses and duration of treatment.

Other hormones can affect melatonin secretion or metabolism. For example, a controlled trial found that a single dose of the synthetic corticosteroid dexamethasone suppressed production of melatonin in nine of 11 healthy volunteers [15, Class I].

Main side effects

The available pharmacologic doses of fast-release melatonin (*eg,* 3 mg) and low-dose slow-release (or controlled) preparations (*eg,* 0.5 mg) tend to increase hormone levels over a 24-hour period, thus altering the circadian pattern of circulating melatonin [16••, Class II]. Abnormally high melatonin levels at night and in the day after consumption of a pharmacologic dose of the hormone may disrupt the delicate mechanism of the circadian system and dissociate mutually dependent circadian body rhythms, which is described in a recent study [17]. Thus, if administered in high doses or at inappropriate times, melatonin may induce a circadian rhythm disorder rather than cure one.

Cost/cost effectiveness

The price of melatonin on the market is relatively low, because of its label of a "food supplement" and its wide availability. Unfortunately, lack of quality and quantity control over the melatonin preparations sold on the US market does not allow estimating its cost or cost effectiveness.

Emerging therapies

- Recent studies suggest that melatonin therapy can be beneficial to children and adults with a wide range of neurologic disorders associated with seizures, mental retardation, attention deficit, and hyperactivity [18••, Class II]. Another potentially important area of melatonin application is anxiety disorders, for example, those associated with acute withdrawal from drug abuse [17,19]. These new emerging applications of melatonin may be related to its anxiolytic, myorelaxant, and hypnotic properties.

Pediatric considerations

- The human fetus and newborn infant do not produce melatonin but rely on the hormone supplied via the placental blood and, postnatally, via the mother's milk. In infants older than 9 to 12 weeks, rhythmic melatonin production increases rapidly; the highest nocturnal melatonin levels are documented in children of 3 to 5 years of age. These data suggest that melatonin may play an important role in development and that prenatal and postnatal melatonin deficiency may have significant negative effects. However, the role of melatonin in development is poorly understood and requires further investigation before compensation of melatonin deficiency during pregnancy or at early age can be recommended.
- Melatonin treatment was successfully applied in children with a number of neurologic disorders, including those affected by Angelman syndrome [18••, Class II; 20••, Class II]. In such children, an increase in sleep quantity and quality after melatonin (0.3 mg) administration was not accompanied by significant changes in their daytime behavior. However, in some patients, parents and teachers noticed a decrease in hyperactivity, and this effect correlated with an increase in the children's attention. Because children with neurologic disorders are often prone to seizures, the reported antiseizure properties of melatonin may provide an additional benefit for such patients. If long-term melatonin treatment in these children is initiated, it is important to use physiologic rather than pharmacologic doses of the hormone, because excess melatonin may affect the development of the reproductive system.

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